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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SGAGIAS, MAGDALENE K	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,616	UPTON ET AL.	
	Examiner	Art Unit	
	MAGDALENE SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28 and 35-38* is/are pending in the application.

4a) Of the above claim(s) *3,4,6,8-20,24-28,35 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7,21-23,37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 09/25/2010 have been fully considered. The amendment to the claims dated 09/25/2010 has been entered. Claims 1-28, 35-38 are pending. Claims 29-34 are canceled. Claims 3-4, 6, 8-20, 24-28, 35-36 are withdrawn. Claims 1-2, 5, 7, 21-23, 37-38 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 1 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to claim 1 dated 09/25/2010.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims **1-2, 5, 7, 21-23, 37-38** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment to claim 1 and its depended claims dated 09/25/2010.

Claim Rejections - 35 USC § 112/Necessitated by Amendment

Claims **1-2, 5, 7, 21-23, 37-38** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118(a) states "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

In the instant case, the amendment by recitation of the limitation… "wherein the synthetic chimeric protein does not comprise an insulin-like growth factor binding protein (IGFBP).."(claim 1) is considered new matter. Upon further review of the instant specification, examiner could only find support for an IGFBP is preferably not present in an IGF-I/VN synthetic chimera. [0095]. However, the examiner could not find support for an IGFBP is preferably not present in an IGF-II/VN synthetic chimera as instantly claimed.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981) teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time application was filed…If a claim is amended to include subject matter, limitation or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes, "When an amendment is filed in reply to an objection or rejection based on U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendment made to the disclosure".

To the extent the claimed compositions are not described in the instant disclosure, claims **1-2, 5, 7, 21-23, 37-38** are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since the applicants disclosure do not teach a composition that is adequately described in the specification. In this case, it appears that the claims reflect a genus of IGFBP. The claims as amended do not have any functional negative characteristics that is a mammalian cell culture medium comprising a synthetic chimeric protein, wherein the synthetic chimeric protein does not comprise an IGFBP in an IGF-II./VN synthetic chimeric protein culture medium. A review of art would indicate that many cell culture media do not comprise a synthetic chimeric protein that does not comprise IGFBP in an IGF-II/VN culture medium, however, it is not synthetic chimeric protein that does not comprise IGFBP in an IGF-II/VN culture medium. Simply providing, for what the synthetic chimeric protein dos not have would constitute an enormous amount of experimentation to empirically test all culture media to determine if it is not synthetic chimeric protein that does not comprise IGFBP in an IGF-II/VN culture medium. As described before, the specification does not provide adequate guidance on determining what is included or excluded by the claims as amended and therefore an artisan of skill would require undue experimentation to practice or make and/or use the invention.

Claim Rejections - 35 USC § 112/Necessitated by Amendment

Claims **1-2, 5, 7, 21-23, 37-38** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendment by recitation of the limitation (b) an av integrin-receptor binding vitronecin (VN) fragment that does not comprise a heparin binding domain (HBD).." (claim 1) does not comply wit written description requirement..

Applicant claims functional fragments of an av integrin-receptor binding vitronecin (VN) fragment that does not comprise a heparin binding domain (HBD. The claims read on a broad genus of sequences.

The written description requirement for a genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicants were in possession of the claimed invention. In the instant case, the specification does not sufficiently describe a representative number of functional fragments of an av integrin-receptor binding vitronecin (VN) fragment that does not comprise a heparin binding domain (HBP) by actual reduction to practice or by disclosure of relevant identifying characteristics.

Applicant claims a functional mutant of VN by function only, without any disclosed or the heparin binding domain (HBD) of VN (and analogously FN) is not required for the full biological activity of isolated protein complexes [0085]; the polyanionic region is amino acid residues 53-64 of the mature VN sequence [0087]; the present invention contemplates embodiments of synthetic chimeric proteins that do not include the HBD and/or the polyanionic region of VN or FN [0088]; and with regard to VN proteins and amino acid sequences thereof that do not include the HBD and/or the polyanionic region, these may be naturally occurring proteins such as the 54 kDa chicken yolk VN (lacking a HBD) or may be engineered by deletion, mutation or truncation

of a VN protein or amino acid sequence so that the HBD and/or the polyanionic region are absent or at least substantially non-functional [0089]. The specification does not teach how to mutate VN and still have it function. The skilled artisan cannot envision a sufficient number of embodiments of the instant invention from the instant specification because the specification only discloses the polyanionic region is amino acid residues 53-64 of the mature VN sequence.

The state of the art at the time of filing does not provide sufficient information on the subject to overcome the deficiencies of the instant specification. There is no description in the art that allows one to envision a representative number of functional mutants by disclosing structural or functional features of VN so that one of skill in the art could envision the claimed invention. Thus the skilled artisan cannot consult the art at the time of filing to envision a sufficient number of embodiments of the instant invention to see that the applicant was in possession of the claimed genus.

Neither the specification of the instant application or the state of the art at the time of filing teaches a structure-function relationship for a representative number of functional mutants. As a result, the skilled artisan would not be able to envision the claimed invention. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-2, 5, 7, 21-23, 37-38 under 35 U.S.C. 103(a) as being unpatentable over Upton et al [WO 02/24219 (IDS)]; Vuori et. al. (US Pat. No. 5,830,504, 1998); Sommer et al, (US Pat. No. 5,407,913, 1995); in view of Klemke et al, (The Journal of Cell Biology, 127: 859-866, 1994); Nam et al (Endocrinology, 143(1): 30–36, 2002) is withdrawn in view of the amendment to claim 1 and its depended claims dated 09/25/2010.

Claims **1-2** are rejected under 35 U.S.C. 102(b) as being anticipated by **Upton et al** [Endocrinology, 140(6): 2928-2931, 1999, (IDS) thereafter referred as Upton 1999] in view of **Nagano et al** [JBC, 267(34): 24863-24870, 1992) (IDS)]; **Nakao et al** (US 5,360,789; date issued; May 20, 1993); **Schvartz et al** (The International Journal of Biochemistry & Cell Biology 31: 539-544, 1999); of **Klemke et al,** (The Journal of Cell Biology, 127: 859-866, 1994 (IDS)).

Upton 1999 teaches vitronectin (VN) binds directly to IGF-II and suggests a role for IGF-II in cell adhesion and invasion (abstract). Upton 1999 teaches amino acid sequencing of the purified VN protein revealed that it has the same N-terminal sequence as chicken vitronectin (VN) (abstract) **(claim 1(a).** Upton 1999 teaches VN specifically bind IGF-II, and the interaction of VN with IGF-II is different to those with other characterized IGF-binding proteins thus, inherently, Upton 1999 does not teach the IGF-II;VN complex comprises an insulin-like growth factor binding protein (IGFBP) (abstract) thus Upton 1999 meets the limitation of the synthetic chimeric protein does not comprise an IGFBP **(claim 1(b).** Upton 1999 teaches that both human and bovine VN also specifically bind IGF-II (abstract). Upton 1999 suggests a role for IGF-II in cell adhesion and invasion (abstract). Upton 1999 suggests the interaction of VN to IGF-II in extracellular matrix where interactions between growth factors and matrix proteins occur and the interaction of VN:IGF-II act as a as "co-receptor" providing a reservoir for growth factors at the cell surface (p 2931, 1st column, 1st paragraph). Moreover, Upton 1999 suggests IGF-II enhances invasion by extravillous trophoblast cells by stimulating migration in invasion

assays in the presence of 1/% FBS and the IGF-II induced migration drastically reduced in serum-free medium (p 2931, 1st column, 1st paragraph) **(claim s1 (ii), claims 2, 5).** Upton 1999 differs from the present invention for not teaching an a_v integrin-receptor binding VN fragment that does not comprise a heparin binding domain (HBD).

However, at the time of the instant invention **Nagano et al** [JBC, 267(34): 24863-24870, 1992)] teach that chicken yolk chicken vitronectin has cell spreading activity but lacks heparin binding activity, thus inherently lacks HBD (p 24868, 2nd column, under discussion 1st paragraph) thus, Nagano teaches the limitation of a VN fragment that does not comprise a heparin binding domain (HBD) **(claim 1 (b).** Nagano teaches yolk vitronectin is homologous with the mammalian vitronectin (abstract). **Nakao et al** (US 5,360,789; date issued; May 20, 1993) teaches VN and IGF-II having a therapeutic effect on skin and corneal diseases, in particular, wounds (column 1, lines 14-35). Nakao teaches VN and IGF-II factor have been known and the healing process of the skin wound is accompanied by granulation tissue formation, angiogenesis and re-epithelization and these processes, fibroblasts, vascular endothelial cells and epidermal cells (keratinocytes) proliferate and migrate, respectively and the VN and IGF-I, IGF-II factors have been known to be effective to the skin healing (column 1, lines 14-35) **(claims 7, 21, -23, 38). Schvartz et al** (The International Journal of Biochemistry & Cell Biology 31: 539-544, 1999) teaches VN contains an RGD sequence, through which it binds to the integrin receptor avb3, and is involved in the cell attachment, spreading and migration (abstract). Schvartz also teaches VN plays a role in wound healing in view of the involvement of the integrin avb3 in angiogenesis (p 543, 2nd column, 1st paragraph). **Klemke et al** teaches that receptor tyrosine kinase signaling required for integrin $\alpha_v\beta5$–directed cell motility but not adhesion on vitronectin (title). Klemke teaches that for wound repair the adhesive interactions between the cells and the extracellular matrix are mediated by integrins receptor on

the surface of the cells and their binding to vitronectin ligand on the extracellular matrix and for wound healing cell motility is required (p 859, 1st column). Klemke teaches that FG cells expressing the $\alpha v\beta 5$ integrin receptor in the presence of EGF in the medium activate the tyrosine kinase pathway which mediates cell motility and not attachment on the vitronectin ligand in the extracellular matrix in vitro (p 860 2nd column bridge to p 861).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Upton 1999 by utilizing vitronectin that does not comprise the HBD such as taught by Nagano and comprises an av integrin receptor binding VN such as taught by Schvartz in

order to increase the cell spreading activity of the complex such as taught by Nagano and in order for VN and IGF-I, IGF-II factors be effective to the skin healing process of the skin wound processes in keratinocytes as taught by Nakao, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to use integrin receptor binding VN in order to produce receptor tyrosine kinase signaling required for integrin-directed cell motility for wound repair since for wound healing cell motility is required and cells expressing the $\alpha v\beta 5$ integrin receptor in the medium activate the tyrosine kinase pathway which mediates cell motility and not attachment on the vitronectin ligand in the extracellular matrix in vitro such as taught by Klemke.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Applicant's arguments are directed to the claim amendments, thus have not been rebut in view of the new rejections necessitated by amendment.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAGDALENE K. SGAGIAS whose telephone number is (571)272-3305. The examiner can normally be reached on 8.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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